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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/355,664	10/08/99	SUNDSTROM M	10806-96

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EXAMINER	
CHERNYSHEV, O	
ART UNIT	**PAPER NUMBER**
1646	10

DATE MAILED: 03/20/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/355,664	Applicant(s) SUNDSTROM ET AL.	
	Examiner Olga N. Chernyshev	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 22-41* is/are pending in the application.

4a) Of the above claim(s) *22-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 October 1999* is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Response to Amendment

1. Claims 11-21 have been cancelled, claim 30 has been amended and claims 31-41 have been added as requested in the Amendment and Response to Restriction and Election Requirements of paper # 9, filed on January 08, 2001. Claims 1-10 and 22-41 are pending in the instant application.

Election/Restrictions

2. Applicant's election with traverse of Group I, claims 1-10 in Paper No. 9 is acknowledged. The traversal is on the ground(s) "that it would not be unduly burdensome for the Examiner to examine claims 11-21 and 26-30 together with elected claims 1-10". This is not found persuasive because of the following reasons. Claims 11-21 and 26-30 of Group II are drawn to crystals of receptor proteins and represent distinct invention, compared to claims 1-10 of Group I, drawn to a cytokine receptor protein itself, which could be used independently in non-crystallized form. M.P.E.P. § 803 provides that the separate classification (i.e., class and subclass) of distinct inventions is sufficient to establish a *prima facie* case that the search and examination of the plural inventions would impose a serious burden upon the Examiner; such separate classification was set forth in the Office action mailed 06 December, 2000 (Paper #8). Applicant has offered no evidence to rebut this showing. Therefore, a *prima facie* case for a serious search burden was presented in Paper #8, and Applicant has offered no evidence to rebut this showing.

The newly added claims 31-42 are clearly directed to crystals of receptor proteins, which corresponds to the non-elected Group II, that is why these claims also represent a patentably distinct invention.

The requirement is still deemed proper and is therefore made FINAL.

Applicant's election the species of modified human growth hormone receptor (hGHR) which consists of the amino acids 32-237 of the native molecule is acknowledged.

Claims 22-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

Claims 1-10 are under examination in this office action.

Priority

3. The instant application was filed as 371 application of PCT/SE98/00277, filed February 17, 1998. The instant specification should contain as the first line of the specification a statement that this application is the national stage entry of PCT/SE98/00277, filed February 17, 1998 as a claim for priority. Correction is required.

Oath/Declaration

4. It appears that at least one full given name of applicant Michael Sundstrom is not present in the signature. This application will not be passed to issue until the omitted name has been supplied or unless a statement has been supplied over the applicant's signature setting forth that the name as signed is the actual full name of applicant Michael Sundstrom. See MPEP § 605.04.

Drawings

5. The drawings filed on October 08, 1999 are acceptable subject to correction of the informalities indicated on the attached "Notice of Draftperson's Patent Drawing Review," PTO-948. In order to avoid abandonment of this application, correction is required.

Specification

6. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

7. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-References to Related Applications.
(c) Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
(e) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(i) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.
(l) Sequence Listing (see 37 CFR 1.821-1.825).

Brief Description of the Drawings is missing. Correction is required.

8. Pages 14-15 include list of references cited. It is suggested that references be included in the text of the specification. If Applicant adopts this suggestion, a substitute specification will be required. Also, reference #20 (or 20/21) on page 14 is confusing, clarification is required.

9. Specification of the instant application contains information presented in a difficult to understand way due to the numerous grammatical errors. The following sentences should be rewritten in order to be understood. Page 6, lines 11-13 "Initially…"; lines 20-22 "It was therefore…"; lines 23-25 "A second generation…". Page 8, lines 14-16 "Therefore…"; lines 19-21 "However,…". Page 9, lines 13-16 "No structure…"; lines 16- 19 "In addition,…"; lines 23-25 "It has also…". Example 1 is mostly incomprehensible due to numerous grammatical errors, incomplete sentences, lack of logic and use of abbreviations and references to unpublished materials. The attempt to incorporate subject matter into this application by reference to "Sundstrom, M. et al. J Biol Chem, in press" is improper because it is not a published reference. It is suggested that Example 1 is completely rewritten.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the modified human growth hormone receptor (hGHR) consisting of

residues 32-237 of the native molecule of hGHR, capable of being crystallized without being complexed to a ligand molecule, does not reasonably provide enablement for a modified extracellular domain of a cytokine receptor protein, capable of being crystallized without being complexed to a ligand molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The present invention relates to modified proteins of extracellular domain of cytokine receptors. The main purpose of the invention is to crystallize these proteins in the pure form, free from their natural ligand molecules. According to specification of the instant application "it has so far been impossible to perform binding studies of hGHR in crystalline form without having the receptor molecule bound to a natural ligand. The reason is that both hGHR and other cytokine receptors have been found difficult to crystallize in their unliganded form" (pages 1-2).

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. In re Wands, 8 USPQ2d, 1400 (CAFC 1988).

The state of the art of crystallized proteins is such that numerous problems exist in achieving desirable results, which is mostly the explanation of the difficulties of crystallizing the proteins of the instant invention. It is well known that the process of protein crystallization depends on various and numerous factors, molecular structure of a protein and precise conditions

for growing particular crystals among them. Even slight variation in the structure or size of a molecule could potentially change the stoichiometry of the forming crystal complex and lead to unpredictable results. For example, as it is stated on page 6 of the specification "despite strenuous efforts all attempts failed to crystallize the native molecule, hGHR 1-237". It is also further indicated that after attempts of crystallizing different receptor variants "One such receptor variant, hGHR 32-234 not only yield crystals of surprisingly good diffraction quality (Table 1) but also displayed surprisingly improved properties with regard to expression levels, solubility and stability during the purification process" (page 6) (emphasis added by the Examiner). Thus, as it is known from the literature and confirmed by the specification of the instant application, crystallization of cytokine receptor proteins is very unpredictable. That is why it is so important for a skilled artisan in order to practice the full scope of claimed invention to have a precise and clear protocol. The instant specification provides no guidance on how to make any modified extracellular domain of a cytokine receptor protein (except for hGHR 32-237), capable of being crystallized without being complexed to a ligand molecule. The specification is mostly devoted to the modified extracellular domain of hGHR crystallization, and the only working example describes the process of producing crystals of hGHR 32-234. Accordingly, there is no working examples presented in the specification that would disclose the parameters for practicing the full scope of the instant invention without undue experimentation. The specification discloses that "Since dimerization of cell surface receptors most likely is a general mechanism to initiate intracellular signal transduction, conformational adaptation of receptor molecules upon ligand binding, as observed in this study, may be applicable to other systems as well. The invention as

described in the appended claims, therefore should be regarded as generalizible beyond the claim scope" (page 10, original grammar and spelling preserved).

Thus, taking into consideration the nature of the invention, the unpredictable art of protein crystallization, the lack of guidance and working examples provided in the specification, it becomes clear that it would require undue experimentation for the skilled artisan to discover how to make and use Applicant's invention, as currently claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Claims 1 and 6 are indefinite because it is not clear what are the metes and bounds of "A modified extracellular domain of a cytokine receptor protein". Is only the extracellular domain present or is the claim to encompass an entire receptor where the extracellular domain is modified? Clarification is required.

13. Claim 3 is indefinite for reciting "molecular segment which contributes to a disordered structure". The metes and bounds of this recitation cannot be determined.

14. Claims 4 and 5 are indefinite because the extent of truncation is not defined.

15. Claim 6 is unclear and indefinite for the recitation "being human growth hormone receptor (hGHR)". It is not clear if a receptor is to modified until it becomes hGHR or if the

starting material is hGHR. A recitation of "wherein the receptor is human growth hormone receptor (hGHR)" may obviate this ground of rejection.

16. Claims 7 and 8 are indefinite because it is not clear in what consequential order amino acid residues are removed from the N- or C-terminal end of the molecule.

17. Claims 9 and 10 are indefinite because it is not clear what is "the native molecule" referred to.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Muller Y.A. et al.

Muller Y.A. et al. teach crystals of the extracellular domain of human tissue factor (hTF). Tissue factor is a member of class II of the cytokines receptor superfamily (page 145, first column, first paragraph). The crystals of hTF developed by Muller Y.A. et al. were free of ligands, only in contact with neighboring molecules (page 150, first column, lines 10-11). The hTF crystals had conformational modifications, as well as different reduced and oxidized forms (page 149, first column, second paragraph). Finally, the crystals of hTF, according to Table 3, page 150, were forming homodimers.

Conclusion

19. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (703) 305-1003. The examiner can normally be reached on Monday to Friday 9 AM to 5 PM ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (703) 308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-0294 for After Final communications.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)0. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 308-4556 or (703) 308-4242. If either of these numbers is out of service, please call the Group receptionist for an alternative number. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Official papers should NOT be faxed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Olga N. Chernyshev, Ph.D. ONC
March 18, 2001

CHRISTINE J. SAOUD
PRIMARY EXAMINER

Christine J. Saoud